III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING INHALATION OF POLLUTANTS AND INFECTION

Chronic bronchitis is a clinical disorder characterized by excessive mucus secretion. It may appear concurrently with pulmonary emphysema, so that the major problem in the diagnosis is to establish that bronchitis is the predominant disease.

As in pulmonary emphysema, cigarette smoking is one of the risk factors in the pathogenesis of chronic bronchitis. Two other risk factors, air pollution and infections, are discussed in this section. At the present time, it is not possible to rank these risk factors in the order of their importance.

The primary concern of this section is chronic bronchitis. The literature on postmortem, clinical and animal investigations relating to chronic bronchitis is reviewed here. Three bibliographic lists are appended:

No. 6. Chronic bronchitis: general aspects.

No. 7. Bronchial carcinoma.

No. 8. Air pollutants and lung disease.

The early cellular changes in the bronchial mucosa and secretion in chronic bronchitis have been confused with metaplasia, so that it is important to exclude consideration of neoplastic disease from the following paragraphs.

1005051356

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-A. POSTMORTEM EXAMINATION

The basic histopathologic change of chronic bronchitis is generalized hypertrophy and hyperplasia of the mucus-secreting bronchial glands throughout the treachea and bronchi. There are also diffuse inflammatory changes consisting principally of increased number of mononuclear cells in the thickened trancheobronchial submucosa and metaplastic epithelial changes with loss of cilia (Reid 1954, 1960; [illegible], [illegible]; Marcatili et al., 1967; Thurlbeck and Angus 1967).

There are only two reports of postmortem examination and known smoking habits of patients with chronic bronchitis. Mitchell et al (1966) reported 64 autopsies, all but one subject having been smokers and 91% for more than 20 pack-years (no of pack daily x years). Niewoehner et al. (1972) reported 4 fatal cases of regional chronic bronchitis, all of the patients having been chronic smokers.

All the other postmortem observations compare the histological features of the bronchi of smokers and nonsmokers, most of them healthy, Chang (1956, 1957, 1958) in 105 random autopsies noted distended goblet cells in 25 out of 71 smokers (35%) but only in 6 out of 34 nonsmokers (17.6%). The average length of cilia was shorter than in nonsmokers and the smokers' epithelium was thicker than that of nonsmokers. The hypertrophy of the bronchial mucus glands, characteristic of chronic bronchitis, has been reported to be more frequent among smokers. The gland/wall ratio was significantly raised

1005051357

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

in 35 heavy smokers, but there was no difference between 23 nonsmokers and 15 moderate (13ss than 20 cigarettes/day) smokers (Thurlbeck et al., 1963). A similar conclusion was arrived at in a larger group of cases, also in Canada like the previous group consisting of 40 nonsmokers and 111 smokers, including 58 heavy smokers (Thurlbeck and Angus, 1964). In another group, reported from England, the mean percentage volume of bronchial mucus glands was significantly greater in 106 smokers than in 73 nonsmokers (Dunnill and Ryder 1971; Ryder et al., 1971). In a smaller group, from Ohio, there was no difference in percentages of such glands between 11 smokers and 13 nonsmokers (Sobonya and Kleinerman, 1972). Ido et al. (1959) reported that percentages of goblet cells increased in light smokers but decreased in heavy smokers.

Squamous metaplasia of bronchial epithelium is commonly seen in various pathologic processes as a result of atypical epithelial regeneration. In 128 unselected autopsies, the general incidence of metaplasia was 32%; the highest incidence was 71% in patients with primary lung carcinoma and the next highest was 41% in patients with chronic inflammatory disease of the lung. In the same group, 39% of nonsmokers had metaplasia and 45% of smokers had a similar epithelial change (Weller, 1955). The subsequent reports show the incidence of metaplasia to be as follows:

Sanderad, 1958	8% of 58 smokers	54% of 39 nonsmokers
Cross et al., 1961	16% of 197 smokers	8% of 33 nonsmokers
Spain, 1969, 1970	65% of 52 smokers	50% of 36 nonsmokers

1005051358

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Auerbach et al. (1961; 1962a, b; 1968) have reported their results in terms of nature of the nucleus relevant to neoplastic changes. Their observations did not include those relating to bronchitis.

The incidence of goblet cell metaplasia is about equal in smokers and nonsmokers (Karpick et al., 1970). The proliferation of epithelial cells has been reported in the palate (Chapman and Redish, 1960) and larynx (Ryan et al., 1955) of smokers.

1005051359

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING INHALATION OF POLLUTANTS AND INFECTION

A. POSTMORTEM EXAMINATION

Reprint

AUERBACH O, STOUT A P, HAMMOND E C and GARFINKEL L: Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Engl J Med 265: 253-67, 1961. 173

AUERBACH O, STOUT A P, HAMMOND E C and GARFINKEL L: Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. N Engl J Med 267: 111-19, 1962A. 174

AUERBACH O, STOUT A P, HAMMOND E C and GARFINKEL L: Bronchial epithelium in former smokers. N Engl J Med 267: 119-25, 1962B. 175

AUERBACH O, STOUT A P, HAMMOND E C and GARFINKEL L: Interrelationships among various histologic changes in bronchial tubes and in lung parenchyma. Am Rev Resp Dis 90: 867-876, 1968. 176

CHANG S C: Studies of bronchial epithelium from smokers and nonsmokers. Proc Am Ass Cancer Res 2: 99-100, 1956. 177

CHANG S C: Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and nonsmokers. Cancer 10: 1246-62, 1957. 178

CHANG S C: Studies of suberepithelial tissue of bronchi from smokers and non-smokers. Proc Am Ass Cancer Res 2: 286-87, 1958. 179

CHAPMAN I and REDISH C H: Tobacco-induced epithelial proliferation in human subject. Arch Path 70: 133-40, 1960. 180

CROSS K R, WALZ D V, PALMER G K and WARNER E D: A study of the tracheobronchial epithelium and changes related to smoking. J Iowa Med Soc 51: 137-40, 1961. 181

DUNNILL S and RUDEN R: A Quantative study of the relationship between chronic bronchitis emphysema and smoking. Chest 59 (5 Suppl): 355-65, 1971. 182

IDE G, SUNTZEEF V and COWDRY E V: A comparison of the histopathology of tracheal and bronchial epithelium of smokers and nonsmokers. Cancer 12: 473-84, 1959. 183

KARPICK R J, PRATT P C, ASMUNDSSON T and KILBURN K H: Pathological findings in respiratory failure. Goblet cell metaplasia, alveolar damage, and myocardial infarction. Ann Intern Med 72: 189-97, 1970. 184

MARCATILI S, BONO M D and ZUCCHETTO C: Comportamento dell'epitelio bronchiale in alcune bronco-pneumopatie chroniche. Riv Anat Patol Oncol 31: 308-30, 1967. 185

MITCHELL R S, RYAN S F, PETTY T L and FILLEY G: The significance of morphologic chronic hyperplastic bronchitis. Am Rev Resp Dis 93: 720-29, 1966. 186

NIEWOEHNER D E, KLEINERMAN J and KNOKE J D: Regional chronic bronchitis. Am Rev Resp Dis 105: 586-93, 1972. 187

REID L M: Pathology of chronic bronchitis. Lancet 1: 275-78, 1954. 188

10050513 60

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Bibliography III-A

Reprint

REID L: Measurement of the bronchial mucous gland layer: a diagnostic yardstick in chronic bronchitis. Thorax 15: 132-41, 1960. 189

RYAN R F, McDONALD J R and DEVINE K D: The pathologic effects of smoking on the larynx. Arch Path 60: 472-80, 1955. 190

RYDER R C, DUNNILL M S and ANDERSON J A: A quantitative study of bronchial mucous gland volume, emphysema and smoking in a necropsy population. J Pathol 104: 59-71, 1971. 191

SANDERUD K: Squamous metaplasia of the respiratory tract epithelium. An autopsy study of 214 cases. Acta Path Microbiol Scand 43: 47-61, 1958. 192

SOBONYA R E and KLEINERMAN J: Morphometric studies of bronchi in young smokers. Am Rev Resp Dis 105: 768-75, 1972. 193

SPAIN D M: The distribution of tracheobronchial metaplasia (regenerative hyperplasia) (age, sex, cigarette smoking and relations to reid index) preliminary report. Pub Health Serv Pub 1879: 183-86, 1969. 194

SPAIN D M, BRADESS V A, TARTER R and MATERO A: Metaplasia of bronchial epithelium. JAMA 211: 1331-34, 1970. 195

THURLBECK W M and ANGUS G E: A distribution curve for chronic bronchitis. Thorax 19: 436-42, 1964. 196

THURLBECK W M and ANGUS G E: The variation of reid index measurements within the major bronchial tree. Am Rev Resp Dis 95: 551-55, 1967. 197

THURLBECK W M, FRASER R G and BATES D V: The correlation between pulmonary structure and function in chronic bronchitis, emphysema and asthma. Med Thorac 22:295-303, 1965. 198

THURLBECK W M, ANGUS G E and PARE J A P: Mucous gland hypertrophy in chronic bronchitis, and its occurrence in smokers. Br J Dis Chest 57: 73-78, 1963. 199

WELLER R W: Metaplasia of bronchial epithelium. A postmortem study. 768-74, 1955. 200

10050513 61

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-B. ANTEMORTEM STUDIES

Chronic bronchitis diagnosed clinically by measurements of lung function is seen both in smokers and in nonsmokers. Simonson (1965) reported a series from Sweden consisting of the following: of 30 males, 2 were nonsmokers and of 35 females 5 were nonsmokers. Half of the patients reported some allergy connection and one-third were exposed to dusts in their occupations.

A coordinated study in four Canadian cities included 216 patients with chronic bronchitis, 2 of whom were nonsmokers. In the follow-up data of the Toronto group, although the patients as a whole showed a decrease in ventilatory function and in diffusing capacity, 10 of the 44 patients had stopped smoking and a further 6 had reduced their cigarette consumption (Bates et al., 1966). No detectable improvement occurred following the reduction of smoking.

1005051362

Of 260 patients with chronic bronchitis reported in Germany there was a higher proportion of nonsmokers than in other countries. Wendel (1968) counted 66 of these patients who were nonsmokers. In England, Simpson (1965) reported that 18 out of 157 patients were nonsmokers, and Caird et al. (1972) stated that out of 47 patients 18 were nonsmokers. In Egypt, Megaked (1966) reported that 8 out 65 bronchitic patients were non-smokers. In the United States, Massaro and Bottoms (1967) noted that 27 out of 327 patients were nonsmokers. The overall incidence of nonsmokers in all these reports is 13% of bronchitic patients.

Source: https://www.industrydocuments.ucsf.edu/docs/qjmk0000

Reports from Japan (Shiota et al., 1966), the United States (Burrows and Earle, 1969; Brinkmann and Block 1968, 1972) and England (Jones et al., 1967; Fletcher, 1968) indicated a high incidence of smokers among patients with chronic bronchitis but the exact figures were not given.

Bronchial biopsy has been performed in patients with chronic bronchitis. There was a higher incidence of mucus gland hypertrophy in smokers than in nonsmokers (Megahed et al., 1967). A few patients with regional bronchitis have been described but the number is too small to allow evaluation of significance of smoking (Anthonisen et al., 1968; Niewoehner et al., 1972).

1005051363

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING, INHALATION OF POLLUTANTS AND INFECTION

B. ANTEMORTEM STUDIES

Reprint

ANTHONISEN N R, BASS H, ORIOL A, PLACE R E G, and BATES D V: Regional lung function in patients with chronic bronchitis. Clin Sci 35: 495-511, 1968. 201

BATES D V, GORDON C A, PAUL G I, PLACE R E G, SNIDAL D P and WOOLF C R: Chronic bronchitis. Report of the third and fourth stages of the co-ordinated study of chronic bronchitis in the department of verterns affairs, Canada. Med Serv J Can :1-59, 1966. 202

BRINKMAN G L, BLOCK D L: The prognosis in chronic bronchitis. Pub Health Serv 1717: 317-26, 1968. 203

BRINKMANN G L, BLOCK D L: Chronic bronchitis in a working population. J Occup Med 14: 825-27, 1972. 204

BURROWS B and EARLE R H: Prediction of survival in patients with chronic airway obstruction. Am Rev Resp Dis 99: 865-871, 1969. 205

CAIRD F I and AKHTAR A J: Chronic respiratory disease in the elderly. A population study. Thorax 27: 764-68, 1972. 206

FLETCHER C M: Prognosis in chronic bronchitis. Pub Health Service 1717: 309-15, 1968. 207

JONES N L, BURROWS B and FLETCHER C M: Serial studies of 100 patients with chronic airway obstruction in London and Chicago. Thorax 22: 327-35, 1967. 208

MASSARO D and BOTTOMS L: Epidemiology of chronic bronchitis. Med Times 95: 121-28, 1967. 209

MEGAHED G E: The role of smoking in chronic bronchitis in Egyptians. J Egypt Med Ass 49: 313-28, 1966. 210

MEGAHED G E, SENNA G A, EISSA M H, SALEH S Z and EISSA H A: Smoking versus infection as the aetiology of bronchial mucous gland hypertrophy in chronic bronchitis. Thorax 22: 271-78, 1967. 211

NIEWOEHNER D E, KLEINERMAN J and KNOKE J D: Regional chronic bronchitis. Am Rev Resp Dis 105: 586-93, 1972. 212

SHITO K, HAMADA A, YASUTARO Y M, EMURA M, MITANI K, MATSUDA M, INOUE T, SAWAL M, KAWAMURA S and OKUBO M: Studies on chronic bronchitis in Osaka. Jap J Med 6: 105-6, 1967. 213

SIMONSSON B G: Clinical and physiological studies on chronic bronchitis. Acta Allergologica 20: 257-300, 1965. 214

SIMPSON T: Chronic bronchitis and emphysema with special reference to prognosis. Br J Dis Chest 62: 57-79, 1968. 215

WENDEL V H: Zur bedeutung des rauchens fur die chronische bronchitis. Zeit Ges Ann Med 23: 147-51, 1968. 216

100505136

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-C. EXAMINATION OF SPUTUM

There is an increase in the amount of expectoration in patients with chronic bronchitis. The observations relating to cigarette smoking consist of the cellular components of the sputum. Vassar et al. (1960) reported an increase in fluorescent histiocytes in the sputum of cigarette smokers which were absent in that of nonsmokers. They suggested that the fluorescence might be due to the presence of polycyclic hydrocarbons bound to the lipid in the cytoplasm of the histiocyte. Roque and Pickren (1968) performed a histochemical study of lung biopsies. In the histiocytes (also known as alveolar macrophages) of smokers there was a loss of oxidoreductases and hydrolases that was directly proportional to the amount of fluorescent material stored in the cells.

Masin and Masin (1966) examined sputum specimens and observed an increase in the proportion of lipophages in the smokers as compared with the nonsmokers. They explained the difference as due to a combined effect of irritation of the alveolar lining, increased turnover of alveolar cells with increased injury to macrophages and shift in the relative proportion of lipophages. Alveolar macrophages obtained by endobronchial lavage of cigarette smokers and nonsmokers were examined with the electron microscope (Pratt et al., 1971). In smokers the inclusions are heterogeneous and measure from 0.1 to 20 μ in diameter; the inclusions in nonsmokers are mostly round or oval and measure from 0.1 to 2.0 μ.

There is an increase in incidence of metaplasia of bronchial epithelial cells in the sputum of smokers (Robbins, 1966; Fullmer, 1968; Nasiell, 1968; Rimingen, 1968). Since metaplasia also occurs in nonsmokers, it is

100501365

Source: https://www.industrydocuments.ucsf.edu/docs/qjmk0000

not possible to attribute to smoking the presence of cells thus affected. Fullmer et al., (1969) observed an increase in incidence of bronchial and bronchiolar spirals, fibrils and casts in smokers who were suffering from chronic bronchitis as compared with nonsmokers.

The other techniques for the examination of sputum concern sputum purulence (Miller, 1963), protein turnover (Bonomo and D'Addabbo, 1964), electrolyte content (Nicolas, 1964) and concentration of neuraminic acid (Reid, 1967). The influence of smoking on these parameters has not been investigated.

1005051366

Source: https://www.industrydocuments.ucsf.edu/docs/qjmk0000

BIBLIOGRAPHY

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING, INHALATION OF POLLUTANTS AND INFECTION

C. EXAMINATION OF SPUTUM

Reprint:

BONOMO L and D'ADDABBO A: Albumin turnover and loss of protein into the sputum in chronic bronchitis. Clinica Chemica Acta 10: 214-22, 1964. 217

FULLMER C D: Microscopic observations of sputum of chronic cigarette smokers. Rocky Mt Med J 65: 13, 1968. 218

FULLMER C D, SHORT J G, ALLEN A and WALKER K: Sputum of chronic cigarette smokers. Rocky Mt Med J 66: 42-46, 1969. 219

MASIN F and MASIN M: Frequencies of alveolar cells in concentrated sputum specimens related to cytologic classes. Acta Cytologica 10: 362-67, 1966. 220

MILLER D L: Study of techniques for the examination of sputum in a field survey of chronic bronchitis. Am Rev Resp Dis 88: 473-83, 1963. 221

NASIELL M: Sputum-cytologic changes in smokers and non-smokers in relation to chronic inflammatory lung diseases. Acta Pathol Microbiol Scand 74: 205-13, 1968. 222

NICOLAS R: Klinisch-experimentelle sputumuntersuchungen bei chronischer bronchitis. Medicina Thoracalis 21: 223-55, 1964. 223

PRATT S A, SMITH M H, LADMAN A J and FINLEY T N: The ultrastructure of alveolar macrophages from human cigarette smokers and nonsmokers. Scand J Clin Lab Invest 24: 331-38, 1971. 224

REID L: Mucus secretion and chronic bronchitis. Medicina Thoracalis 24: 40-43, 1967. 225

RIMINGTON J: Smoking, sputum, and lung cancer. Br Med J 1: 732-34, 1968. 226

ROBBINS W T: Bronchial epithelium in smoking and non-smoking college students. J Am Coll Health Assoc 14: 265-66, 1966. 227

ROQUE A L and PICKREN J W: Enzymatic changes in fluorescent alveolar macrophages of the lungs of cigarette smokers. Acta cytologica 420-29, 1968. 228

VASSAR P S, CULLING C and SAUNDERS A M: Fluorescent histiocytes in sputum related to smoking. Arch Pathol 70: 649-52, 1960. 229

100505136?

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-D. AIR POLLUTANTS AS A RISK FACTOR

The role of air pollutants in the pathogenesis of chronic bronchitis is discussed in the articles listed in bibliographic list no. 8. Briefly, the association of this condition with air pollutants is similar to that with cigarette smoking. There is a parallel relationship between the incidence of chronic bronchitis and either the degree of pollution in the air or the amount of cigarette smoking (Anderson 1962).

The incidence of chronic bronchitis in the general population has been correlated with the following indices of air pollution. Fairbairn and Reid (1958) reported that among London postmen disablement and death were related to the frequency of fog and presumably the level of air pollution. Schoettlin (1962) observed that the prevalence of chronic bronchitis among elderly males was higher among those exposed to five occupational factors: cooking fats, gasoline and oils, coal dust and welding fumes. Among American male college students the incidence of chronic bronchitis detected by evaluation of respiratory function was correlated significantly with ambient temperature (Spodnik et al., 1966). Levels of sulfur dioxide in the air showed a positive correlation with incidence of respiratory illness in the United States (McCarroll et al., 1967; Heimbach, 1971).

1005051368

The importance of air pollution and cigarette smoking has been assessed by some investigators. Winkelstein (1969), Motley (1971),

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Motley and Yanda (1966) and Cohen et al. (1972) have the opinion that cigarette smoking is more significant than air pollution in causing chronic bronchitis. Their evidence is not based on a comparison with subjects free from exposure to pollutants. The experience of Phelps and Koike (1962) in the Tokyo-Yokohama episode of asthmatic bronchitis is unique in that American soldiers who were heavy smokers were exposed to air pollutants. After they were transferred to the United States, although they continued smoking, their bronchitis was relieved. In this episode, air pollution is more important than cigarette smoking in causing bronchitis.

100505136

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING, INHALATION OF POLLUTANTS AND INFECTION

D. AIR POLLUTANTS AS A RISK FACTOR

Reprint

ANDERSON R J: Epidemiologic studies of air pollution. Dis Chest 42: 474-81, 1962. 230

COHEN C A, HUDSON A R, CLAUSEN J L and KNELSON J H: Respiratory symptoms, spirometry, and oxident air pollution in nonsmoking adults. Am Rev Resp Dis 105: 251-61, 1972. 231

FAIRBAIRN A S and REID D D: Air pollution and other local factors in respiratory disease. Br J Prev Soc Med 12: 94-103, 1958. 232

HEIMBACH J A Jr: The correlation of polluted air with tree growth and lung disease in humans. Compr Biol Med 1: 243-53, 1971. 233

McCARROLL J, CASSELL E J, WOLTER D W, MOUNTAIN J D, DIAMOND J R and MOUNTAIN I M: Health and the urban environment. V. Air pollution and illness in a normal urban population. Arch Environ Health 14: 178-83, 1967. 234

MOTLEY H L: Clinical aviation and aerospace medicine. Environmental air pollution effect on pulmonary function. Aerosp Med 42: 1108-10, 1971. 235

MOTLEY H L and YANDA R: Environmental air pollution, emphysema and ionized air. Dis Chest 50: 343-52, 1966. 236

PHELPS H W and KOIKE S: Tokyo-Yokohama Asthma. The rapid development of respiratory distress presumable due to air pollution. Am Rev Resp Dis 86: 55-63, 1962. 237

SCHOETTLIN C E: The health effect of air pollution on elderly males. Am Rev Resp Dis 86: 878-97, 1962. 238

SPODINK M J Jr, CUSHMAN G D, KERR D H, BLIDE R W and SPICER W S: Effects of environment on respiratory function. Arch Environ Health 13: 243-54, 1966. 239

WINKELSTEIN W Jr, and KANTOR S: Respiratory symptoms and air pollution in an urban population of northeastern United States. Arch Environ Health 18: 760-67, 1969. 240

10050513?0

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-E. INFECTION AS A RISK FACTOR

The basic lesion in chronic bronchitis is inflammation, which is largely due to pathogens. The infectious process may either be the primary cause of the inflammation or may supercede the initial irritation of the bronchial mucosa by chemical substances. There are defence mechanisms which protect the bronchial passages from bacterial or viral infections (see reviews by Green, 1968 a, b, and Rylander, 1969). The process of clearance of bronchial passages is accomplished by the ciliated epithelium and the mucus-secreting goblet cells. The effect of cigarette smoking on mucociliary clearance is discussed in Section VI. The next paragraphs discuss the influence of cigarette smoking on the bronchial infections, which in turn would lead to chronic bronchitis.

The incidence of the common cold is not higher in smokers than in nonsmokers (Kler, 1945). Amon 143 allergic subjects between 18 and 35 years of age, who were challenged with infectious secretions taken from patients with a common cold, 45% developed colds as compared with 31% among 693 nonallergic individuals, who were inoculated in the same way. Amon both groups of subjects, 35% of smokers and 34% of nonsmokers developed colds, indicating that smoking did not influence the susceptibility to the common cold (Dowling et al., 1957). This is the most important evidence that smoking does not increase the susceptibility to the common cold.

Prevalence studies have produced the opposite conclusion. On the basis of symptoms of acute repiratory infections, the following groups show

100505371

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

a higher incidence among smokers than nonsmokers: 118 adults residing in Cleveland (Boake, 1958); 175 student nurses in Canada (Parnell et al., 1966); 191 high school students in New Jersey (Haynes et al., 1966); 1,811 male college students in South Carolina (Finklea et al., 1969).

There are other observations relating to the influence of smoking on the incidence of bronchial infections. Air pollution has been shown by Douglas and Waller (1966) to relate to frequency of respiratory infection in children residing in London. The antibacterial activity of the saliva is enhanced by thiocyanate ion which may be absorbed from cigarette smoke (Courant, 1967). Patients with pulmonary emphysema show an elevation of immunoglobulin A(Ig A) in the blood, which has been interpreted as a sign of the presence of bronchopulmonary infection (Biegel and Krumholz, 1968). The concentration of immunoglobulin A in the saliva is also elevated in patients with chronic pulmonary disease, but this was not influenced by cigarette smoking (Lewis et al., 1970). In the same study cigarette smoking suppressed production of immunoglobulin A in the saliva of normal subjects. These observations on immunoglobulin do not explain the association between cigarette smoking and respiratory infections.

1005051372

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING INHALATION OF POLLUTANTS AND INFECTION

E. INFECTION AS A RISK FACTOR

Reprint

BIEGEL A A and KRUMHOLZ R A: An immunoglobulin abnormality in pulmonary emphysema. Am Rev Resp Dis 97: 217-22, 1968. 241

BOAKE W C: A study of ilness in a group of Cleveland families. XVIII. Tobacco smoking and respiratory infections. N Engs J Med 259: 1245-49, 1958. 242

COURANT P: The effect of smoking on the antilactobacillus system in saliva. Odontol Revy 18: 251-61, 1967. 243

DOUGLAS J W B and WALLER R E: Air pollution and respiratory infection in children. Br J Prev Soc Med 20: 1-8, 1966. 244

DOWLING H F, JACKSON G G and INOUYE T: Transmission of the experimental common cold in volunteers. II. The effect of certain host factory upon susceptibility. J Lab Clin Med 50: 516- 25, 1957. 245

FINKLEA J F, SANDIFER S H and SMITH D D: Cigarette smoking and epidemic influenza. Am J Epidemiol 90: 290-99, 1969. 246

GREEN G M: Pulmonary antibacterial mechanisms and the pathogenesis of pulmonary disease. Yale J Biol Med 40: 414-29, 1968A. 247

GREEN G M: Pulmonary clearance of infectious agents. Ann Rev Med 19: 315-36, 1968B. 248

HAYNES W F Jr, KRSTULOVIC V J and BELL A L L: Smoking habit and incidence of respiratory tract infections in a group of adolescent males. Am Rev Resp Dis 93: 730-35, 1966. 249

KLER J H: An analysis of colds in industry. Trans Am Acad Ophthalmol Otolaryngol 201-7, 1945. 250

LEWIS D M, LAPP N L and BURRELL R: Quantitation of secretory immunoglobulin A in chronic pulmonary disease. Am Rev Resp Dis 101: 55-61, 1970. 251

PARNELL J L, ANDERSON D O and KINNIS C: Cigarette smoking and respiratory infections in a class of student nurses. New Engl J Med 274: 979-84, 1966. 252

RYLANDER R: Environmental air pollutants and lung defense to airborne bacteria. Pub Health Serv Pub 1879: 297-304, 1969. 253

1005051373

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

III-F. ANIMAL EXPERIMENTS RELATING TO CHRONIC BRONCHITIS

There is no available model in the laboratory which mimics the pathological and functional features of the human form of chronic bronchitis. The reported experiments pertain to one of several underlying processes in chronic bronchitis, such as mucus secretion, bronchial epithelial changes, nature of the alveolar lining and the influence of infection (see reviews by Pattle, 1958, 1965 and Green, 1968 and 1969). There are no reported measurements of pulmonary function in these animals to validate the claim that the experiments can be applied to elucidate the effects of cigarette smoking in man.

1. Rabbit. Proetz (1939) reported the first observations on the effect of cigarette smoke on the airways of the rabbit. By visual examination he noted the accumulation of tar, chiefly in the nasal cavity. Holland et al. (1958, 1963) impregnated cigarettes with radioactive arsenic to trace absorption of smoke in the rabbit. Exposure for one to two years caused pathological changes in the respiratory epithelium of the nose and tracheobronchial mucosa, but no measurements were made prior to sacrificing the animals. The remaining observations in the rabbit relate to the alveolar macrophages investigated in vitro (Heese and Myrvik, 1967; Myrvik and Evans, 1967; Weissbecker et al., 1969). The water-soluble constituents of cigarette smoke depress protein synthesis in rabbit alveolar cells (Yeager, 1969). The depressant action of cigarette smoke on phagocytic activity of alveolar macrophages may be prevented by gluthathione and cysteine (Green and Carolyn, 1967; Green, 1968 a, b).

1005051374

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

2. Guinea pig. Rylander (1968, 1969) used the guinea pig to investigate the pulmonary defence mechanism against airborne bacteria. Animals exposed to cigarette smoke showed a reduction in the number of radioactive bacteria killed, as compared with the controls. This was interpreted as an effect of smoke on the mucus flow which clears the lung. There was no difference in the reduction of viable bacteria, indicating that the efficiency of the bactericidal mechanisms had not been impaired. In a subsequent report, Rylander (1971) described a reduction in the number of free lung cells in the fluid used for lavaging the airways. However, after two to four weeks of exposure there was an increase in the number of macrophages. This biphasic response indicates a tolerance to the reduction of cells in response to cigarette smoke. An increase in the number of pulmonary cells from chronic exposure has been reported by Flint et al. (1971). The depression of oxidative phosphorylation of pulmonary cells noted by Kyle and Riesen (1970) after 2 1/2 days' exposure needs to be examined in animals exposed for several weeks.

3. Rat. Exposure of the rat to cigarette smoke for six weeks produced an increase in the number of goblet cells in the trachea and intrapulmonary airways (Lamb and Reid, 1969). The effect cannot be induced by inhalation of extremes of temperature, indicating that this is not the important factor in smoke which increases the number of goblet cells (Jones et al., 1971). The addition of phenylmethyloxadiazole to the tobacco protected the rat from the increase in goblet cell count. This was the first effective means of protection found against changes produced in bronchial epithelium by tobacco smoke (Jones et al., 1972). The condition of pulmonary

100505137S

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

macrophages in response to air pollutants other than cigarette smoke has been studied by Gross et al. (1969).

4. Mouse. Leuchtenberger et al. (1958, 1960) and Leuchtenberger and Leuchtenberger (1965) reported the cytochemical and cytological alteration in the bronchi of mice exposed to cigarette smoke. The presence of bronchitis was diagnosed by appearance of proliferative epithelial changes and metaplasia. These changes relate to carcinogenesis rather than to bronchitis. There is a decrease in bacterial clearance following an acute exposure to cigarette smoke (Laurenzi et al., 1963). There is an increase in susceptibility to naturally acquired infection of the respiratory tract in mice exposed to cigarette smoke (Wynder et al., 1968). In experiments on mice challenged with Klebsiella pneumoniae or Diplococcus pneumoniae, the decrease in resistance was shown to be transitory. When the time interval between smoke exposure and infectious challenge was lengthened from 1 to 48 hours, there was no demonstrable decrease in resistance to respiratory infection (Spurgash et al., 1968).

1005051376

5. Dog. Auerbach et al. (1967) and Frasca et al. (1968 a, b) reported the histological and ultrastructural changes in the bronchial epithelium of dogs exposed to cigarette smoke for 24 to 421 days. The atypical nuclei noted in the epithelium do not relate to chronic bronchitis and are beyond the scope of this review.

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

III. CHRONIC BRONCHITIS: CONCURRENCE OF CIGARETTE SMOKING, INHALATION OF POLLUTANTS AND INFECTION

F. ANIMAL EXPERIMENTS RELATING TO CHRONIC BRONCHITIS

Reprint

AUERBACH O, HAMMOND E C, KIRMAN D, GARFINKEL L and STOUT A P: Histologic changes in bronchial tubes of cigarette-smoking dogs. Cancer 20: 2055-66, 1967. 254

FLINT G L, MAXWELL K W and RENZETTI A D: Influence of cigarette smoke on guinea pigs. Effect on pulmonary cells and serum antitrypsin levels. Arch Environ Health 22: 366-69, 1971. 255

FRASCA J M, AUERBACH O, PARKS V R and JAMIESON J D: Electron microscopic observations of the bronchial epithelium of dogs. I. Control Dogs. Exp Mol Pathol 9: 363-79, 1968A. 256

FRASCA J M, AUERBACH O, PARKS V R and JAMIESON J D: Electron microscopic observations of the bronchial epithelium of dogs. II. Smoking dogs. Exp Mol Pathol 9: 380-99, 1968B. 257

GREEN G M: Protection of alveolar macrophages from the cytotoxic activity of cigarette smoke by glutathione and cysteine. J Clin Invest 47: 42a-43a, 1968A. 258

GREEN G M: Pathophysiology of the alveolar macrophage system. Public Health Serv 1786: 463-80, 1968B. 259

GREEN G M: Cigarette smoke: protection of alveolar macrophages by glutathione and cysteine. Science 162: 810-11, 1968C. 260

GREEN G M: The response of the alveolar macrophage system to host and environmental changes. Arch Environ Health 18: 548-50, 1969. 261

GREEN G M and CAROLIN D: The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. N Engl J Med 276: 421-27, 1967. 262

GROSS P, deTREVILLE T P, TOLKER E B, KASCHAK M and BABYAK M A: The pulmonary macrophage response to irritants. Arch Environ Health 18: 174-85, 1969. 263

HEISE E R and MYRVIK: Secretion of lysozyme by rabbit alveolar macrophages in vitro. J Reticuloendothel Soc 4: 510-23, 1967. 264

HOLLAND R H, KOZLOWSKI E J and BOOKER L: The effect of cigarette smoke on the respiratory system of the rabbit. Cancer 16: 612-15, 1963. 265

HOLLAND R H, WILSON R H, MORRIS D, McCALL M S and LANZ H: The effect of cigarette smoke on the respiratory system of the rabbit. Cancer 11: 709-12, 1958. 266

JONES R, BAETJER A M and REID L: Effect of extremes of temperature and humidity on the goblet cell count in the rat airway epithelium. Br J Ind Med 28: 369-73, 1971. 267

JONES R, BOLDUC P and REID L: Protection of rat bronchial epithelium against tobacco smoke. Br Med J 2: 142-44, 1972. 268

100505137?

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

KYLE J L and RIESEN W H: Stress and cigarette smoke effects on lung mitochondrial phosphorylation. Arch Environ Health 21: 492-97, 1970. 269

LAMB D and REID L: Goblet cell increase in rat bronchial epithelium after exposure to cigarette and cigar tobacco smoke. Br Med J 1: 33-35, 1969. 270

LAURENZI G A, GUARNERI J L, ENDRIGA R B and CAREY J P: Clearance of bacteria by the lower respiratory tract. Science 142: 1572-73, 1963. 271

LEUCHTENBERGER V C and LEUCHTENBERGER R: Kumulative wirkung von zigaretenrauch-inhalation und influenza-virus-infektion bei der entstehung von atypischen proliferationen im bronchialepithel von mausen. Oncologia 19: 81-104, 1965. 272

LEUCHTENBERGER C, LEUCHTENBERGER R and DOOLIN P F: A correlated histological cytological and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. I. Bronchitis with atypical epithelial changes in mice exposed to cigarette smoke. Cancer 11: 490-526, 1958. 273

LEUCHTENBERGER C, LEUCHTENBERGER R, ZEBRUN W and SHAFFER P: A Correlated histological cytological and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. II. Varying responses of major bronchi to cigarette smoke, absence of bronchogenic carcinoma after prolonged exposure, and disappearance of bronchial lesions after cessation of exposure. Cancer: 13: 721-32, 1960. 274

MYRVIK Q N and EVANS D G: Metabolic and immunologic activities of alveolar macrophages. Arch Environ Health 14: 92-96, 1967. 275

PATTLE R E: Properties, function, and origin of the alveolar lining layer. Proc R Soc Biol 148: 217-40, 1958. 276

PATTLE R E: Surface lining of lung alveoli. Physiol Rev 45: 48-79, 1965. 277

PROETZ A: Some preliminary experiments in the study of cigarette smoke and its effects upon the respiratory tract. Ann Otol 48: 176-94, 1939. 278

RYLANDER R: Pulmonary defence mechanisms to airborne bacteria. Acta Physiol Scand Suppl 306: 1-89, 1968. 279

RYLANDER R: Alterations of lung defence mechanisms against airborne bacteria. Arch Environ Health 18: 551-55, 1969. 280

RYLANDER R: Free lung cell studies in cigarette smoke inhalation experiments. Scand J Resp Dis 52: 121-28, 1971. 281

SPURGASH A, EHRLICH R and PETZOLD R: Effect of cigarette smoke on resistance to respiratory infection. Arch Environ Health 16: 385-91, 1968. 282

WEISSBECKER L, CARPENTER R D, LUCHSINGER P C and OSDENE T S: In vitro alveolar macrophage viability. Effect of gases. Arch Environ Health 18: 756-59, 1969. 283

WYDNER E L, TAGUCHI K T, BADEN V and HOFFMANN D: Tobacco carcinogenesis. IX. The effect of cigarette smoke on respiratory tract of mice after passive inhalation. Cancer 21: 134-53, 1968. 284

1005051378

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Bibliography III-F

Reprint

YEAGER H Jr: Alveolar cells: depressant effect of cigarette smoke on protein synthesis. Proc Soc Exp Biol Med 131: 247-50, 1969. 285

10050513 29

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

IV. PULMONARY EMPHYSEMA-BRONCHITIS COMPLEX

Pulmonary emphysema-bronchitis complex, also known as chronic obstructive pulmonary disease, is discussed in this section separately from the sections dealing with its individual components (Sections II and III). It has been the practice of the United States Public Health Service to base their mortality statistics on a combination of pulmonary emphysema and chronic bronchitis even though separate death rates are available. It appears that combining the two entities under a single name has improved the results of statistical analysis in establishing the high incidence of deaths from pulmonary disease among smokers as compared with nonsmokers. The publications relating to the pulmonary emphysema-bronchitis complex are contained in additional bibliographic lists as follows:

No. 9. Pulmonary emphysema-bronchitis complex: etiology and pathology.

No. 10. Pulmonary emphysema-bronchitis complex: clinical studies.

Most of the publications in the above-mentioned lists emphasize the difference between the two entities, but the practice of combining both in mortality statistics has not been discontinued in the United States and has also been adopted in foreign countries.

1005051380

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

IV-A. MORTALITY STATISTICS IN THE UNITED STATES

In 1958 Dorn reported the mortality experience of male policy holders of U. S. Government Life Insurance during the 2 1/2-year period 1954-1956. The death rate for persons who had smoked regularly was 36% greater than that for persons who had never smoked. Expressed in another way, with 1.00 as the death rate of nonsmokers, , that of smokers was 1.36. The mortality ratios for the diseases of the lung were as follows: cancer of the lung, 9.85, chronic obstructive pulmonary disease, 3.27. It was on this basis that the United States Public Health Service founded their conclusion that cigarette smoking causes cancer of the lung and chronic obstructive pulmonary disease. The mortality ratio of deaths from coronary heart disease was 1.63 and it is on this lower ratio that cigarette smoking was regarded as a risk factor. It will be noted that the mortality ratio of chronic lung disease is closer to that of heart disease than to that of lung carcinoma, so that it would have been more logical to draw a similar conclusion for chronic lung disease and heart disease. The subsequent publications of Dorn (1959, 1960, 1961), Kahn (1961) and Weir and Dunn (1970) recounted these mortality ratios and called attention to the declining death rate from disease of the respiratory system since 1900 (from 26% in 1900 to 8% in 1959). However, during the past decade the death rate increased significantly for a group of chronic respiratory diseases, including chronic bronchitis, emphysema, fibrosis and pneumonia.

1005051381

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

The second mortality study, in which 1,078,894 persons were enrolled, was conducted by the American Cancer Society in 1959 and 1960. The mortality rate was higher for smokers than for nonsmokers. The mortality ratio for the pulmonary emphysema-bronchitis complex among smokers as compared with nonsmokers was 3.27 (Hammond and Horn, 1958; Hammond, 1959, 1964, 1966). The details of the statistical analysis of the mortality figures are contained in the publications relating to Smoking and Health. The regional analyses have been published separately for Georgia (Hammond and Letton, 1965), Illinois (Hammond and Street, 1964), Iowa (Hammond and Stocks, 1964), Kansas (Hammond et al., 1964), Minnesota (Hammond et al., 1965), Missouri (Hammond and Wilson, 1965), New York State (Hammond et al., 1965), and Ohio (Hammond and Gerber, 1965). The similarities in the mortality statistics of these areas have been emphasized but their dissimilarities have been ignored.

10050513 82

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

IV. PULMONARY EMPHYSEMA-BRONCHITIS COMPLEX

A. MORTALITY STATISTICS IN THE UNITED STATES

	Reprint
DORN H F: The mortality of smokers and nonsmokers. Am Stat Ass Proc Soc Stat Sec 34-71, 1958.	286
DORN H F: Tobacco consumption and mortality from cancer and other diseases. Public Health Report 74: 581-73, 1959.	287
DORN H F: Tobacco consumption and mortality from cancer and other diseases. Acta Un Int Cancer 16: 1653-65, 1960.	288
DORN H F: The increasing mortality from chronic respiratory diseases. Am Stat Ass Proc Soc Stat Sec 148-52, 1961.	289
HAMMOND E C: Discussion. Am Stat Ass Proc Soc Stat Sec 60-64, 1959.	290
HAMMOND E C: Smoking in relation to mortality and morbidity. Findings in first thirty-four months of follow-up in a prospective study started in 1959. J Natl Cancer Inst 32: 1161-88, 1964.	291
HAMMOND E C: Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr 19: 127-204, 1966.	292
HAMMOND E C, BERGLUND L and KASLOW R: Smoking habits and disease in Minnesota. Minn Med 48: 44-49, 1965.	293
HAMMOND E C, FENT L S, REED D C and WILSON J L: Smoking habits and health in Kansas and other central states. J Kansas Med Soc 65: 586-90, 1964.	294
HAMMOND E C and GERBER L F: Smoking habits and disease in Ohio: Ohio State Med J 61: 134-37, 1965.	295
HAMMOND E C and HORN D: Smoking and death rates -- report on forty-four months of follow-up of 187,783 men. JAMA 166: 1298-1308, 1958.	296
HAMMOND E C and LETTON A H: Smoking habits and health in Georgia and other Southern states. J Med Assoc Ga 54: 278-81, 1965.	297
HAMMOND E C and STOCKS A: Smoking habits and health in Iowa and neighboring states. J Iowa Med Soc 54: 563-67, 1964.	298
HAMMOND E C and STREET E C: Smoking habits and disease in Illinois. Illinois Med J 126: 661-65, 1964.	299
HAMMOND E C, GRIETHUYSEN T H V, DIBELER J B, SNEDDON A M and HALLIGAN W: Smoking habits and disease in New York State. New York State J Med 65: 2557-61, 1965.	300
HAMMOND E C and WILSON O: Smoking habits and disease in Missouri. Missouri Med 62: 109-12, 122, 1965.	301

10050513 83

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Bibliography IV-A

Reprint

JAMES G and ROSENTHAL T: Tobacco and health. Charles C Thomas, Springfield, 1961, pp172-90. 302

KAHN H A: The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observations. Natl Cancer Inst Monogr 19: 1-125, 1966. 303

MILLS C A: Tobacco smoking: Some hints of its biologic hazards. Ohio State Med J 46: 1165-70, 1950. 304

WEIR J M and DUNN J E Jr: Smoking and mortality: a prospective study. Cancer 25: 105-12, 1970. 305

1005051384

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

IV-B. MORTALITY STATISTICS IN FOREIGN COUNTRIES

The frequency of fatal chronic pulmonary disease varies in different countries (Reid and Fletcher, 1971). There is a wide range in the sex ratio of death in males and females, from 2.0 in Japan to 9.9 in Finland, with Canada, Great Britain and the United States between the extremes. These variations do not relate entirely to differences in cigarette consumption but indicate the association of other factors, some identified and others unidentified.

1. Canada. A questionnaire sent to 92,000 veterans from 1956 to 1962 revealed a higher death rate from pulmonary disease among both smokers and nonsmokers (Canadian Department of National Health and Welfare, 1966; Best et al.[a, b, c], 1967). The mortality ratio for all smokers as compared with nonsmokers was 1.33. The ratios for specific diseases were as follows: lung cancer, 14.91; bronchitis and emphysema, 8.71; and coronary heart disease, 1.60. The results of this survey were included in the report of the United States Public Health Service. As in the United States, an increasing number of deaths in Canada during the past decade have been due to chronic obstructive disease. The provincial statistics vary in the assignment of deaths due to pulmonary emphysema. Manitoba having the highest proportion of deaths caused by emphysema and Ontario the highest proportion of deaths due to chronic bronchitis. Cigarette consumption when expressed per person (15 years of age and over) does not correlate with the distribution of chronic pulmonary obstructive disease (Anderson, 1963, 1968).

1005051385

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

2. Great Britain. The results of a questionnarie sent to 59,600 physicians indicate a relationship between cigarette smoking and mortality rates (Doll and Hill, 1964 a, b). A total number of 111 physicians died of chronic bronchitis. The standardized death rates per 1,000 were as follows: all men, 0.34; nonsmokers, 0.05; all smokers, 0.37; cigarette smokers, 0.51; mixed smokers, 0.33; and pipe or cigar smokers, 0.15. The death rate of smokers is higher than that of nonsmokers. It was recognized by the authors in an earlier report (1956) that some of the excess mortality among cigarette smokers might be due to a tendency to diagnose chronic bronchitis rather than some other respiratory disease in patients with a chronic cough.

3. Israel. The mortality statistics attributed to chronic bronchitis or to emphysema from 1960 to 1964 have been reviewed by Cohen (1967). There has been a rise in such deaths, which are more frequent among immigrants from Africa and Asia than among those from Europe. The author attempted to relate the differences among immigrants to smoking habits surveyed in 1958. The heavy smokers, those using more than 20 cigarettes daily, constituted 27% of all smokers emigrating from Asia and Africa, and 17% of those from Europe. The interpolation of results from another decade has been questioned. Cigarette smoking is not the most important factor accounting for the difference, because the frequency of lung cancer did not show a parallel distribution. The author concluded that the incidence of malnutrition and infection among immigrants from Asia and Africa is a more important factor in contributing to the higher incidence of lung disease.

100051386

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

IV. PULMONARY EMPHYSEMA-BRONCHITIS COMPLEX

B. MORTALITY STATISTICS IN FOREIGN COUNTRIES

Reprint

ANDERSON D O: Observations on the classification and distribution of pulmonary emphysema in Canada. Can Med Ass J 89: 709-16, 1963. 306

ANDERSON D O: Geographic variation in deaths due to emphysema and bronchitis in Canada. Can Med Ass J 98: 231-41, 1968. 307

BEST E W R, WALKER C B, BAKER P M, DELAQUIS F M, McGREGOR J T and McKENZIE A C: Summary of a Canadian study of smoking and health. Can Med Ass J 96: 1104-8, 1967. 308

CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE: Trends in death rates for diseases of interest in relation to smoking, Canada 1950 to 1964. 1966a 309

CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE: A Canadian study of smoking and health pp 1-7, 1966b 310

CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE: A Canadian study of smoking and health. pp 41-50, 1966c 311

COHEN J: Chronic bronchitis and emphysema. Observations on trends and distribution according to death certificate data, Israel 1960 to 1964. Israel J Med Sci 3: 885-89, 1967. 312

DOLL R and HILL A B: Mortality in relation to smoking: ten years' observations of British doctors. Br Med J 1: 1399-1410, 1964A. 313

DOLL R and HILL A B: Mortality in relation to smoking: ten years' observations of British doctors. Br Med J 1: 1460-67, 1964B. 314

REID D D and FLETCHER C M: International studies in chronic respiratory disease. Br Med Bull 27: 59-68, 1971. 315

10050513B7

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

IV-C. CRITIQUE OF MORTALITY STATISTICS

There are four considerations in accepting the mortality statistics of chronic lung disease to support the thesis that cigarette smoking is one of the important causes of pulmonary emphysema, and chronic bronchitis. They are as follows:

1. Sources of error in filing death certificate. The determination of the cause of death is based on the opinion of the physician signing the certificate. The postmortem examination and the clinical picture would establish the diagnosis of pulmonary emphysema or chronic bronchitis. However, the majority of the certificates state the cause of death on the basis of symptomatology, which may not necessarily identify the cause of death. The increase in mortality is dependent to a great extent upon more frequent diagnosis based on incomplete pulmonary function tests and symptomatology rather than upon a true increase in incidence (Barach, 1964; Barach and Segal, 1968; Barach, 1971). For pulmonary emphysema Rosenblatt (1970, 1972) explained the increase in mortality to be an artifact produced by revision of the International List of Causes of Death in 1949, permitting emphysema to be accepted as a primary cause of death. The widespread publicity given to emphysema in scientific and popular publications and the Social Security compensation for disability from emphysema contribute to the record of the sudden increase of deaths from this disease.

2, Influence of air pollution on mortality statistics. The mortality statistics for the entire United States have been handled in their entirety,

1005051388

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

ignoring important regional differences. There are differences in death rates from pulmonary emphysema and chronic bronchitis which relate to socioeconomic classes, provided that concentrations of air pollutants remain constant (Zeidberg et al., 1967). Comparison of mortality statistics in selected areas of the United States with differences in the level of air pollution reveal that environmental pollutants are important in influencing the death rate (Winkelstein et al., 1967; Buell et al., 1967; Hickey et al., 1967). In Great Britain the incidence of mortality rate from chronic bronchitis is correlated significantly with the level of air pollution (Fry, 1954; Pemberton and Goldberg, 1954; Reid, 1956; Crofton, 1965).

3. Factors influencing prognosis of chronic bronchitis and pulmonary emphysema. The most widely known factor that influences the prognosis of a patient with chronic pulmonary disease is cigarette smoking. There are other factors that are equally important and even more so, such as age, sex, geographical altitude, occurrence of cardiac complications, and extent of respiratory insufficiency (Burrows and Earle, 1964; Mitchell et al., 1964; Renzetti et al., 1966; Sukumalchantra et al., 1966; Renzetti, 1967; Tanner, 1967; Asmundsson and Kilburn, 1969; Davis and McClement 1969; Markush, 1969). The role of each of these factors in determining the longevity of patients with chronic pulmonary disease has been determined, but their importance relative to cigarette smoking is not known.

4. Inherent characteristics of cigarette smokers. It has been stated in Section II that smokers may have genetic factors which account for the higher incidence of pulmonary emphysema as compared with nonsmokers.

100505389

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

Although some have been identified, others have not. In a recent study the low incidence of pulmonary emphysema among Seventh Day Adventists, has been explained largely by the fact that they are nonsmokers (Dysinger and Lemon, 1963; Lemon and Walden, 1966). The possibility that members of the families of this religious order may have inherited a trait that renders them resistant to pulmonary disease has not been excluded. The mortality encountered in alcoholics has been reported to be associated with a high incidence of smoking (Rankin et al., 1969). Excessive drinkers are usually heavy smokers (Bailey et al., 1969). Although there are known common causes of death in the alcoholic, chronic pulmonary disease is not one of them. Opium smokers develop chronic obstruction (Da Costa et al., 1971, 1972). The extent of alcoholism and drug abuse has not been considered in the case of smokers dying of chronic pulmonary disease.

1005051390

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

BIBLIOGRAPHY

IV. PULMONARY EMPHYSEMA-BRONCHITIS COMPLEX

C. CRITIQUE OF MORTALITY STATISTICS

	Reprint
ASMUNDSSON T and KILBURN K H: Survival of acute respiratory failure. A study of 239 episodes. Ann Intern Med 70: 471-85, 1969.	316
BAILEY M B, HABERMAN P W and SHEINBERG J: Identifying alcoholics in population surveys. Millbank Mem Fund Quart 47: 235-49, 1969.	317
BARACH A L: Pulmonary emphysema: Pathogenesis and the illusion of increased incidence. Med Counterpoint 3: 40-43, 1971.	318
BARACH A L: Physical exercise in breathless subjects with pulmonary emphysema, including a discussion of cigarette smoking. Dis Chest 45: 113-28, 1964.	319
BARACH A L and SEGAL M S: The increased recognition and incidence of chronic bronchitis and pulmonary emphysema. Ann Allergy 26: 353-57, 1968.	320
BUELL P, DUNN J E and BRESLOW L: Cancer of the lung and Los-Angeles-type air pollution. Cancer 20: 2139-47, 1967.	321
BURROWS B and EARLE R H: Course and prognosis of chronic obstructive lung disease. N Engl J Med 280: 397-404, 1964.	322
CROFTON E C: A comparison of the mortality from bronchitis in Scotland and in England and Wales. Br Med J 1: 1635-39, 1965.	323
DA COSTA J L, TOCK E P C and BOEY H K: Lung disease with chronic obstruction in opium smokers in Singapore. Thorax 26: 555-71, 1971.	324
DYSINGER P W and LEMON F R: Pulmonary emphysema in a non-smoking population. Dis Chest 43: 17-25, 1963.	325
DA COSTA J L, TOCK E P C and BOEY H K: Chronic obstructive lung disease in Singapore. Am Rev Resp Dis 106: 246-59, 1972.	326
DAVIS A L and McCLEMENT J H: The course and prognosis of chronic obstructive pulmonary disease. Pub Health Serv Pub 1879: 219-34, 1969.	327
FRY J: Chronic bronchitis in general practice. Br Med J 1: 190-94, 1954.	328
HICKEY R J, SCHOFF E P and CLELLAND R C: Relationship between air pollution and certain chronic disease death rates. Arch Environ Health 15: 728-38, 1967.	329
LEMON F R and WALDEN R T: Death from respiratory system disease among seventh-day adventist men. JAMA 198: 137-46, 1966.	330
MARKUSH R E: National chronic respiratory disease mortality study. II Mortality associated with persistent cough and phlegm in the United States, 1963. J Chronic Dis 21: 737-48, 1969.	331
MITCHELL R S, WEBB N C and FILLEY G F: Chronic obstructive bronchopulmonary disease. III Factors influencing prognosis. Am Rev Resp Dis 89: 878-96, 1964.	332
PEMBERTON J and GOLDBERG C: Air pollution and bronchitis. Br Med J 2: 567-70, 1954.	333

10050139

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000

RANKIN J G, HALE G S, WILKINSON P, O'DAY D M, SANTAMARIA J N and BABARCZY G: Relationship between smoking and pulmonary disease in alcoholism. Med J Australia 1: 730-33, 1969. 334

REID DD: Symposium: Chronic bronchitis. Proc Royal Soc Med 49: 767-71, 1956. 335

RENZETTI A D Jr: Prognosis in chronic obstructive pulmonary disease. Med Clin NAm 51: 363-71, 1967. 336

RENZETTI A D Jr, McCLEMENT J H and LITT B D: The Veterans administration cooperative study of pulmonary function. Mortality in relation to respiratory function in chronic obstructive pulmonary disease. Am J Med 41: 115-29, 1966. 337

ROSENBLATT M B: Validity of emphysema mortality data. Rev Allergy 24: 1019-22, 1970. 338

ROSENBLATT M B: Emphysema: historical perspective. Bull N Y Acad Med 48: 823-41, 1972. 339

SUKUMALCHANGRA Y, DINAKARA P and WILLIAMS M H Jr: Prognosis of patients with chronic obstructive pulmonary disease after hospitalization for actue ventilatory failure: A three-year follow-up study. Am Rev Resp Dis 93: 215-22, 1966. 340

TANNER E: The prognosis of respiratory diseases. Proc 9th int Congr Life Ass Med 330-43, 1967. 341

WILKELSTEIN W Jr, KANTOR S, DAVIS E W, MANERI C S, and MOSHER W E: The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in man. Arch Environ Health 14: 162-71, 1967. 342

ZEIDBERG L D, HORTON R J M and LANDAU E: Mortality from diseases of the respiratory system in relation to air pollution. Arch Environ Health 15: 214-24, 1967. 343

1005051392

Source: https://www.industrydocuments.ucsf.edu/docs/qfmk0000